REMARKS

For convenience, in the present response, Applicants will refer the Examiner to disclosure in the specification by referencing the appropriate paragraph numbers of the Substitute Specification that was submitted on May 3, 2002.

Status of the claims

Upon entry of these remarks, claims 85-91, 118-124, 148-180, and 183-194 will be pending in this application. New claims 187-194 have been added. Support for these claims may be found in the specification as filed, for example in paragraphs [0439] and [0442]. Accordingly, no new matter has been added and Applicants respectfully request entry of claims 187-194.

Objections to the Specification

The status of U.S. Patent Applications listed in paragraph [0001] and [0895] has been updated. Applicants submit these amendments address the Examiner's objections to the specification set forth in paragraph 3 of the Office Action mailed June 3, 2004. Applicants respectfully request these objections be reconsidered and withdrawn.

Additionally, Applicants have provided the same information as was previously presented in the table in the middle of paragraph [0001] in text format. This amendment adds no new matter. Applicants respectfully request entry of this amendment.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner maintained the rejection of claims 85-91, 118-124, 148-180 and 183-186 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner subdivides the maintained rejection into 5 parts detailed in sections (i)-(v) in the Office Action mailed June 3, 2004. Applicants address the Examiner's comments below.

Rejections set forth in sections (i), (ii), and (iii) of the Office Action mailed June 3, 2004.

Each of sections (i), (ii), and (iii) of the Office Action address the enablement of the claims with respect to administration of the claimed antibody. Specifically, in section (i) the Examiner states:

> The specification does not disclose the optimal quantity, duration, and route of administration of an antagonistic anti-neutrokine-alpha antibody (see pages 180-201 of the specification; paragraphs [0052-0053]). There is also little guidance in the specification for one skilled in the art to determine these optimal conditions. Such trial and error experimentation is considered undue. A large quantity of experimentation would still be required by one skilled in the art to determine the optimal quantity, duration, and route of administration of an anti-neutrokine-alpha antibody to treat all possible autoimmune diseases or disorders, rheumatoid arthritis, and inhibition of B cell proliferation, differentiation, or survival. (see paragraph spanning pages 4-5 of the Office Action mailed June 6, 2004).

In section (ii), the Examiner reiterates the rejection quoted above (see lines 8-11 of page 6 of the Office Action mailed June 6, 2004) and states that the "present invention is unpredictable and complex" and therefore requires more than a single embodiment to be fully enabled. In section (iii), the rejection is rephrased in question form (see paragraph spanning pages 7-8 of the Office Action mailed June 6, 2004) in light of possible problems an anti-Neutrokine-alpha antibody may have in contacting its antigen or problems that may be encountered if the antibody has "non-optimal systemic half-life".

Applicants remind the Examiner of the standard set forth in section 2164.01(c) of the M.P.E.P., (8th edition, revision 2) which states that:

> If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana,* 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).
>
> **For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation.** If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. The applicant need not demonstrate that the invention is completely safe. See also M.P.E.P. § 2107.01 and § 2107.03. (emphasis added)

Applicants maintain their position that one of skill in the art could readily determine the optimal route, quantity and duration of administration of an antagonistic-anti-Neutrokine alpha antibody for the treatment of autoimmune diseases. Beginning with the knowledge of the

biological activity of a molecule (in this case the inhibition of Neutrokine-alpha mediated activities, such as stimulation of B cell proliferation and immunoglobulin secretion), one of skill in the art would know how to proceed to determine the optimal dose, route and duration of administration. Applicants note there is no requirement for the invention to be "optimized."

In support of this assertion Applicants direct the Examiner's attention to the Baker et al. publication cited as reference D1 on the PTO-SB/08 submitted herewith (herein after the "Baker reference"). This publication describes experiments performed by Human Genome Sciences that were used to support a successful Investigational New Drug (IND) Application for the use of an antagonistic anti-Neutrokine-alpha antibody for the treatment of Autoimmune Disease (in which systemic lupus erythematosus is the first indication targeted). The authors of this paper illustrate the routine process of preclinical development of an antagonistic-anti-Neutrokine-alpha antibody (referred to as "LymphoStat-B" in the Baker reference beginning from the knowledge of the basic pharmacologic effects of Neutrokine-alpha (referred to as "BLyS" in the Baker reference). Preclinical studies begin with confirmation of the biological activity of the anti-Neutrokine-alpha antibody in *in vitro* and *in vivo* models. For example, LymphoStat-B was selected based on its ability to neutralize human BLyS induced proliferation of murine splenocytes using an assay similar to the one described in Example 6 of the specification (see first full paragraph in the left hand column of page 3258 of the Baker reference). The ability of LymphoStat-B was further tested to for its ability to neutralize the effects of human BLyS administration to mice (see page 3260-3261 of the Baker reference). In this experiment, a comparison of the effects of administration of 0.3 mg of recombinant BLyS (similar to that described in Example 6 of the specification) to the effects of co-administration of BLyS and LymphoStat-B at doses ranging from 0.05 to 5.0 mg/kg was made. At page 3261, the authors report that:

> Subcutaneous administration of 0.3mg/kg of human BLyS for four consecutive days resulted in increases in spleen weights, in the representation of CD45R+(B220+)/ThB+ splenocytes and in total serum IgA concentrations. Coadministration of LymphoStat-B intravenous resulted in a dose dependent inhibition of these human BLyS induced effects, with complete inhibition observed between 1.5 and 5.0 mg/kg of monoclonal antibody.

Prior to submitting the IND application for phase I trials in humans, a standard good laboratory practice monkey toxicology and pharmacokinetics study was performed. This study is briefly described in the Baker reference in the section spanning pages 3261 and 3262. The

doses used in this study (5, 15 and 50 mg/kg) were chosen based on the doses used in the mouse studies and the doses (0.5 and 5mg/kg) used in another monkey study using an antibody related, but not identical to, LymphoStat-B. Specifically, Human Genome Sciences' IND application stated "[t]he low dose (5 mg/kg) was selected based upon the absence of adverse effects at this dose in the [first] pilot monkey study...The high dose in this study (50 mg/kg administered 4 times at 7 day intervals) was at least 2.5 fold the highest anticipated clinical dose." (See Exhibit A containing a partially redacted section 8.2.2.5.1 of Human Genome Sciences' Investigational New Drug Application (IND) to the Federal Drug Administration for "LymphoStat-B™, BLyS™ Antagonist:Monoclonal Anti-BLyS Antibody for The Treatment of Autoimmune Diseases"). The high dose was chosen to greatly exceed the highest dose planned in humans so as to ensure that any toxic side effects of LymphoStat-B would be observed. More detailed discussion of the results of this study than those reported in the Baker reference were described in Human Genome Science LymphoStat-B IND application (see Exhibit A).

Additionally, a pharmacokinetic study was performed in monkeys to evaluate the distribution and clearance of LymphoStat-B drug product in monkeys. Briefly, eight monkeys (4 male/4 female) received a single intravenous injection of LymphoStat-B at either 5 or 50 mg/kg, and serum concentrations were monitored over nine weeks. LymphoStat-B concentrations in serum samples were determined with a sandwich type ELISA that utilized BLyS for capture and biotinylated anti-human antibody for detection. Serum concentration data were fitted to a 2-compartment pharmacokinetic model using the software package WinNonlin (Pharsight Corp., Mountain View, CA). Immunogenicity was evaluated as well to aid in the interpretation of the pharmacokinetic data. The pharmacokinetic data obtained from the above described monkey study was then used to predict pharmokinetics in humans based on standard interspecies scaling parameters. (See Exhibit B containing a partially redacted sections 8.3.1.1-8.3.1.3 of Human Genome Sciences' Investigational New Drug Application (IND) to the Federal Drug Administration for "LymphoStat-B™, BLyS™ Antagonist:Monoclonal Anti-BLyS Antibody for The Treatment of Autoimmune Diseases", for a description of the conclusions drawn from the pharmacokinetic analysis.)

Together, this data supported a dosing rationale of 1-20 mg/kg in human patients administered as either a single intravenous (iv) infusion or 2 iv infusions spaced 21 days apart in phase I (safety) clinical trials in human SLE patients. Specifically, Human Genome Sciences' IND application for LymphoStat-B states, "[t]he intravenous route for dosing was chosen for the

nonclinical and clinical studies because the iv route of administration maximizes systemic exposure and the target antigen, BLyS, is known to be present in the blood of humans and cynomolgus monkeys. The [phase I] clinical schedule of a single-dose or 2 doses 3 weeks apart was selected based upon the finding that 4 weekly doses of LymphoStat-B up to 50 mg/kg was well tolerated in cynomolgus monkeys." Applicants note that the dose and route of administration used in Human Genome Sciences' phase I clinical trials are supported by the specification in, for example, paragraphs [0439] and [0442]. The results of the phase I study were described in a poster presentation for the 2003 American College of Rheumatology Annual Meeting held in Orlando, Florida which is cited as reference D2 on the PTO-SB/08 submitted herewith.

Frequency and duration of the administration will ultimately be determined by the pharmacokinetics of the antibody in the patient and the patient's response to treatment. Treatment will continue as long as the patient continues to receive therapeutic benefit from it. Applicants would like to make it clear that the discussion above is an example of the routine work those of skill in the art perform to move the development of a therapeutic antibody from the pre-clinical to clinical stage. Other modes of modes of administration (e.g. subcutaneous delivery), doses, and/or dosing schedules, could also be developed.

Applicants submit that work of the type described above, though extensive, would not require undue experimentation by those of skill in the art. Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 443 F.2d 1386, 1390-1391, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). As stated by the Examiner, the factors that can be considered in determining whether an amount of experimentation is undue have been set forth in *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The test for undue experimentation is not merely quantitative, since "a considerable amount of experimentation is permissible, if it is merely routine" *Id* (citing *In re Jackson*, 217 USPQ 804 (Board of Patent Appeals and Interferences, 1982)).

In re Wands involved an appeal from the Board of Appeals and Patent Interferences, affirming the examiner, rejecting immunoassay claims on the grounds that making anti-HBsAg antibodies for use in the claimed immunoassay, other than the deposited antibody, would be "unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies." *Id.* at 735, 8 U.S.P.Q.2d at 1402. Antibodies other than the one

deposited were described only in terms of function and only a general method of making and using them was disclosed in the application. *See Id.* The facts showed that IgM antibodies were disfavored because they tended to self-aggregate and precipitate, isolating the correct antibodies required screening hundreds of clones, and the appellant's first four attempts were unsuccessful. *See Id* at 734, 8 U.S.P.Q.2d at 1402. Nevertheless, the Federal Circuit found that the disclosure satisfied the requirements under 112, first paragraph. The court based its decision on the fact that the invention could be practiced with "readily available starting materials using methods that are well known in the monoclonal antibody art" and because "practitioners of the art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *See Id.* at 736, 8 U.S.P.Q.2d at 1406.

Applicants maintain that the invention could be practiced with readily available starting materials using methods that were well known in the art on the priority date of the instant application. Like the technolology involved in *In re Wands,* practitioners developing therapeutic antibodies are prepared to undertake the long, arduous and expensive, but necessary steps to routinely perform tests in animal models and/or human subjects to determine the optimal route, dose and duration of administration to determine the most safe and preferred treatment regimen.

As Judge Rich explained in *In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to *determine*, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility" (emphasis provided). Because methods of determining the optimal quantity, duration and route of administration of an antibody were known in the art as of the earliest effective priority date of the present application, Applicants submit that one skilled in the relevant art could *determine*, without undue experimentation, the optimal route, dose and duration of administration of an antagonistic anti-Neutrokine-alpha antibody, the enablement requirement is fully satisfied. *In re Wands*, 858 F.2d at 738, 8 U.S.P.Q.2d at 1404; *Ex parte Mark*, 12 U.S.P.Q.2d 1904, 1906-1907 (B.P.A.I. 1989).

In view of the foregoing Applicants respectfully request that the Examiner reconsider and withdrawn this aspect of rejection under 112, first paragraph.

Rejection set forth in section (iv) of the Office Action mailed June 3, 2004.

Applicants have had trouble distinctly identifying exactly what rejection is set forth in section (iv) of the Office Action mailed June 3, 2004. The statement in the first full sentence of page 9 of the Office Action seems to indicate that the rejection relates to either administration of an antibody or the treatment of autoimmune diseases. If it is the former, Applicants believe this aspect of the rejection is addressed above, if it is the latter, this aspect of the rejection is responded to in the following section.

Rejection set forth in section (v) of the Office Action mailed June 3, 2004.

In the Office Action mailed June 3, 2003, the Examiner asserted that the specification does not enable one of skill in the art to treat "all possible autoimmune disorders...which have different pathophysiologies." Increased B cell activity is not the only characteristic of autoimmune diseases and Neutrokine-alpha is not the only stimulant of B cells, particularly B cells directed to produce antibodies to self antigens as in autoimmune diseases." (see page 9, lines 6-9 of the Office Action mailed June 3, 2003.)

In response Applicants submitted a declaration by David Hilbert, an immunologist with greater than 18 years of research experience. In his declaration, Dr. Hilbert explains:

- that autoimmune diseases result from the activity of autoreactive B and T lymphocytes and that the pathologies observed in autoimmune diseases result from damage inflicted by autoreactive cytotoxic T cells (T_{CTL}) and/or autoantibodies secreted by autoreactive B lymphocytes (See paragraphs 3-4 of Hilbert Declaration);
- that even though different autoimmune diseases may have different pathologies, every autoimmune disease involves a common mechanism, i.e., autoreactive B and/or T cell activity (See paragraphs 3-4 of Hilbert Declaration);
- that many autoimmune diseases are treated with non-specific immunosupressant therapies (See paragraph 5 of Hilbert Declaration);
- that Neutrokine-alpha acts on T cells as well as B cells, but even if it did not act on T cells, why Neutrokine-alpha activity on B cells may also influence T cell activity (See paragraphs 6-15 of Hilbert Declaration);
- that immunologists would find it credible that an antagonistic anti-Neutrokine-alpha antibody, by inhibiting Neutrokine-alpha's function as a lymphocyte costimulatory molecule, would be useful in the treatment of a large number of autoimmune diseases

in much the same way immunosuppressants are useful in the treatment of autoimmune diseases with varying pathophysiologies (See paragraph 17 of Hilbert Declaration);

- that many scientists in the field have commented on the use of Neutrokine-alpha antagonists such as antagonistic anti-Neutrokine-alpha antibodies in treating autoimmune diseases as a *class*(See paragraph 16 of Hilbert Declaration).

While it is evident that the Examiner has read Dr. Hilbert's Declaration, the Examiner simply dismissed the rejection as not being persuasive and reiterated her previous rejection that "B cell activity is not the only characteristic of autoimmune diseases and Neutrokine-alpha is not the only stimulant of B cells" and that an anti-Neutrokine-alpha antibody would not be able to "treat all possible autoimmune diseases because each disease has other steps/mechanisms" (see Office Action mailed June 3, 2004, page 10, lines 14-20). Both of these statements fail to respond to Dr. Hilbert's statements that Neutrokine-alpha acts on T cells as well as B cells, and even if it did not, antagonism of Neutrokine-alpha would also be able to dampen T cell-mediated autoimmunity. Applicants submit that the Examiner has not responded to the points made in the Hilbert Declaration as is required. M.P.E.P. (8th edition, Revision 2) at §716.01 states:

> Evidence traversing rejections>, when timely presented,< must be considered by the examiner whenever present. All entered affidavits, declarations, and other evidence traversing rejections are acknowledged and commented upon by the examiner in the next succeeding action. The extent of the commentary depends on the action taken by the examiner. Where an examiner holds that the evidence is sufficient to overcome the *prima facie* case, the comments should be consistent with the guidelines for statements of reasons for allowance. See MPEP § 1302.14. Where the evidence is insufficient to overcome the rejection, **the examiner must specifically explain why the evidence is insufficient.** (emphasis added)

The Examiner also makes note of the fact that the Hilbert Declaration was authored by an employee of Human Genome Sciences which therefore made Dr. Hilbert "an interested party." Applicants remind the Examiner that while a declarant's interest is a factor which may be considered in evaluating expert opinion, a declaration cannot be disregarded solely for the reason that it was authored by an interested party; moreover, a declaration by an interested party may be relied upon when sufficiently convincing. Cf. *In re McKenna* 203 F.2d 717, 720 (C.C.P.A. 1953).

Accordingly, Applicants respectfully request that the Examiner reconsider the Hilbert Declaration and explain why the declaration is not sufficient should she maintain the aspects of the rejection addressed in the Declaration. Applicants submit that this Declaration shows by reasoned argument and factually supported statements that one of skill in the art would find the present application enabling with respect to the treatment of autoimmune diseases and therefore, the application meets the enablement requirement. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this aspect of rejection under 112, first paragraph.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present Amendment be entered and made of record in the present application.

In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance. An early Notice of Allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to Deposit Account No. 08-3425.

Dated: December 2, 2004

Respectfully submitted,

By Michele Shannon

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KKH/MS/ba

A

Investigational New Drug Application

LymphoStat-B™, BLyS™ Antagonist

Monoclonal Anti-BLyS Antibody Therapy for the Treatment of Autoimmune Disease

Serial Number: 000

ITEM 8 PHARMACOLOGY AND TOXICOLOGY

SPONSOR: HUMAN GENOME SCIENCES, INC.

8.2.2.5.1 LymphoStat-B 4-Week GLP Monkey Toxicology Study with 4-Week Recovery

Four groups of 5 male and 5 female experimentally naïve monkeys were treated for 4 consecutive weeks. LymphoStat-B was administered once a week by intravenous injection at 4 dose levels (0, 5, 15, and 50 mg/kg). Three monkeys/gender/dose were necropsied after 4 weeks of treatment (Day 29). Two monkeys/gender/dose were necropsied after a 4-week treatment free period (Day 57).

The low dose (5 mg/kg) was selected based upon the absence of adverse effects at this dose in the pilot monkey study (Section 8.2.3.1.1). The highest dose in the Phase 1 clinical trial is not planned to exceed 20 mg/kg. The high dose in this study (50 mg/kg administered 4 times at 7 day intervals) was at least 2.5 fold the highest anticipated clinical dose.

The study endpoints included the following:

- Clinical observations, including ophthalmic examinations and electrocardiograms
- Clinical pathology, including hematology, clinical chemistry, coagulation parameters and terminal urinalysis
- Evaluation of multidose pharmacokinetics of LymphoStat-B
- Evaluation of immunogenicity of LymphoStat-B
- Complete necropsy, gross examination and histopathologic evaluation of tissues
- Due to the specific and potentially immunosuppressive nature of LymphoStat-B, additional study endpoints were incorporated into the study design.
  - Serum Immunoglobulins (IgM, IgG, IgA)
  - Flow cytometric evaluation of peripheral blood mononuclear cells
  - Flow cytometric evaluation of select tissues (spleen and mesenteric lymph node)

The study demonstrated no clinical signs of toxicity, changes in body weight, food consumption, electrocardiogram, ophthalmoscopy, peripheral blood mononuclear cell populations (total lymphocytes, B lymphocyte subsets, T-lymphocyte subsets or monocytes) or clinical pathology parameters (serum chemistry, hematology, coagulation or urinalysis) that were attributed to LymphoStat-B.

Treatment-related findings included:

- Minimal to mild lymphocyte depletion in B-cell areas of mesenteric lymph node and ileal GALT by histopathology on Day 29
- Decreased percentage of B-cells (CD20+ and CD20+/CD21+) in spleen and mesenteric lymph node by flow cytometry in low dose (5 mg/kg) monkeys at Day 29 and in all treated monkeys on Day 57
- Anti-LymphoStat-B antibodies were detected in one mid-dose (15 mg/kg) and 2 high-dose (50 mg/kg) monkeys. Anti-LymphoStat-B antibodies did not alter the PK of LymphoStat-B in affected monkeys.

Changes that were not clearly treatment-related included:

- Decreased serum IgA in high-dose (50 mg/kg) monkeys on Day 57
- Increased percentage of T-cells in spleen and mesenteric lymph node by flow cytometry at Days 29 and 57
- Increased serum IgG in the high-dose (50 mg/kg) group on Day 15, and decreased serum IgG in the mid-dose (15 mg/kg) group on Day 57

- An abscessed spleen (Day 29) and a mandibular lymph node necrotizing granuloma (Day 57) observed in 2 different high-dose (50 mg/kg) monkeys
- Minimal to mild thyroid follicular epithelial degeneration observed in 3 of 6 high-dose (50 mg/kg) monkeys on Day 29 and in 1 of 4 low-dose (5 mg/kg) and 1 of 4 high-dose (50 mg/kg) monkeys on Day 57

B

Investigational New Drug Application

LymphoStat-B™, BLyS™ Antagonist

Monoclonal Anti-BLyS Antibody Therapy for the Treatment of Autoimmune Disease

Serial Number: 000

ITEM 8 PHARMACOLOGY AND TOXICOLOGY

SPONSOR: HUMAN GENOME SCIENCES, INC.

8.3.1.1 Pharmacokinetics of LymphoStat-B in Cynomolgus Monkey

In order to characterize the pharmacokinetics of LymphoStat-B, a single-dose pharmacokinetic study was conducted in cynomolgus monkeys. Immunogenicity was evaluated as well to aid in the interpretation of the pharmacokinetic data. Eight monkeys (4 male/4 female) received a single intravenous injection of LymphoStat-B at either 5 or 50 mg/kg, and serum concentrations were monitored over nine weeks. LymphoStat-B concentrations in serum samples were determined with a sandwich type ELISA that utilized BLyS for capture and biotinylated anti-human antibody for detection. Serum concentration data were fitted to a 2-compartment pharmacokinetic model using the software package WinNonlin (Pharsight Corp., Mountain View, CA). Pharmacokinetic parameters for LymphoStat-B in cynomolgus monkeys are summarized in Table 14 and serum concentration data for individual monkeys are plotted in Figure 19.

Three out of eight monkeys in the single-dose pharmacokinetic study were positive for anti-LymphoStat-B antibodies. All 3 positive monkeys were in the 50 mg/kg dose group. Two of the monkeys were weakly positive, and their pharmacokinetics did not appear to be affected by the presence of anti-LymphoStat-B antibodies. However, one monkey was strongly positive for anti-LymphoStat-B antibodies, and LymphoStat-B was undetectable by ELISA in the serum of this monkey after Day 15. This monkey was therefore not included in the pharmacokinetic analysis.

The pharmacokinetics of LymphoStat-B following iv injection are biphasic with the β, or elimination, phase contributing approximately 95% of the total area under the concentration curve (AUC). Clearance (CL), initial volume of distribution (V_i), steady-state volume of distribution (V_{ss}), half-life of the alpha and beta phases ($t_{1/2\alpha}$, $t_{1/2\beta}$), and mean residence time (MRT) are independent of dose, whereas AUC and C_{max} are proportional to dose. The pharmacokinetics of LymphoStat-B thus appear to be linear over the range of doses tested. In addition, there were no significant differences in the serum concentrations of LymphoStat-B between male and female monkeys.

The terminal half-life of LymphoStat-B in cynomolgus monkeys is 11-14 days, and the clearance is 5.6 mL/day/kg. This value of CL is substantially less than the glomerular filtration rate for cynomolgus monkeys (3120 mL/day/kg; Schaer et al, 1990), as expected for a large molecule such as an antibody (MW ~150 kDa) (Gobburu et al, 1998). The initial volume of distribution of LymphoStat-B is approximately 44 mL/kg, or about the same as the plasma volume (40 mL/kg; Levine, 1990), and the V_{ss} is 85-107 mL/kg. The relatively small value for V_{ss} compared to the extracellular fluid volume (~170 mL/kg including plasma; Levine, 1990) suggests that LymphoStat-B localizes primarily in the plasma compartment and the interstitial fluid spaces of more permeable tissues.

Table 14 Pharmacokinetic parameters for LymphoStat-B following single iv injection

Parameter	5 mg/kg	50 mg/kg	P value
n	4	3[a]	NA
AUC (day-μg/mL)	901 ± 40	8970 ± 320	< 0.0001
C_{max} (μg/mL)	111 ± 1.8	1230 ± 180	0.0007
$t_{1/2\alpha}$ (day)	0.522 ± 0.13	0.436 ± 0.2	0.7235
$t_{1/2\beta}$ (day)	11.2 ± 0.7	14 ± 1.8	0.1528
CL (mL/day/kg)	5.6 ± 0.2	5.6 ± 0.2	0.9753
V_i (mL/kg)	45.0 ± 0.7	42.4 ± 5.9	0.6286
V_{ss} (mL/kg)	85.0 ± 2.1	108 ± 14	0.1260
MRT (day)	15.4 ± 1.0	19.1 ± 2.1	0.1387

Values are means ± standard error.
[a]One animal was not included in the pharmacokinetic analysis due to a significant drop in serum concentration levels after Day 8. This animal was strongly positive for anti-LymphoStat-B antibodies.
A 3-way ANOVA of serum concentration data comparing males to females yields p=0.4327
AUC, Area Under the Curve; C_{max}, Maximum Concentration; $t_{1/2\alpha}$, Half-life of alpha-phase; $t_{1/2\beta}$, Half-life of β-phase; CL, Clearance; V_i, Initial Volume of Distribution; V_{ss}, Steady-State Volume of Distribution; MRT, Mean Residence Time; NA, not applicable

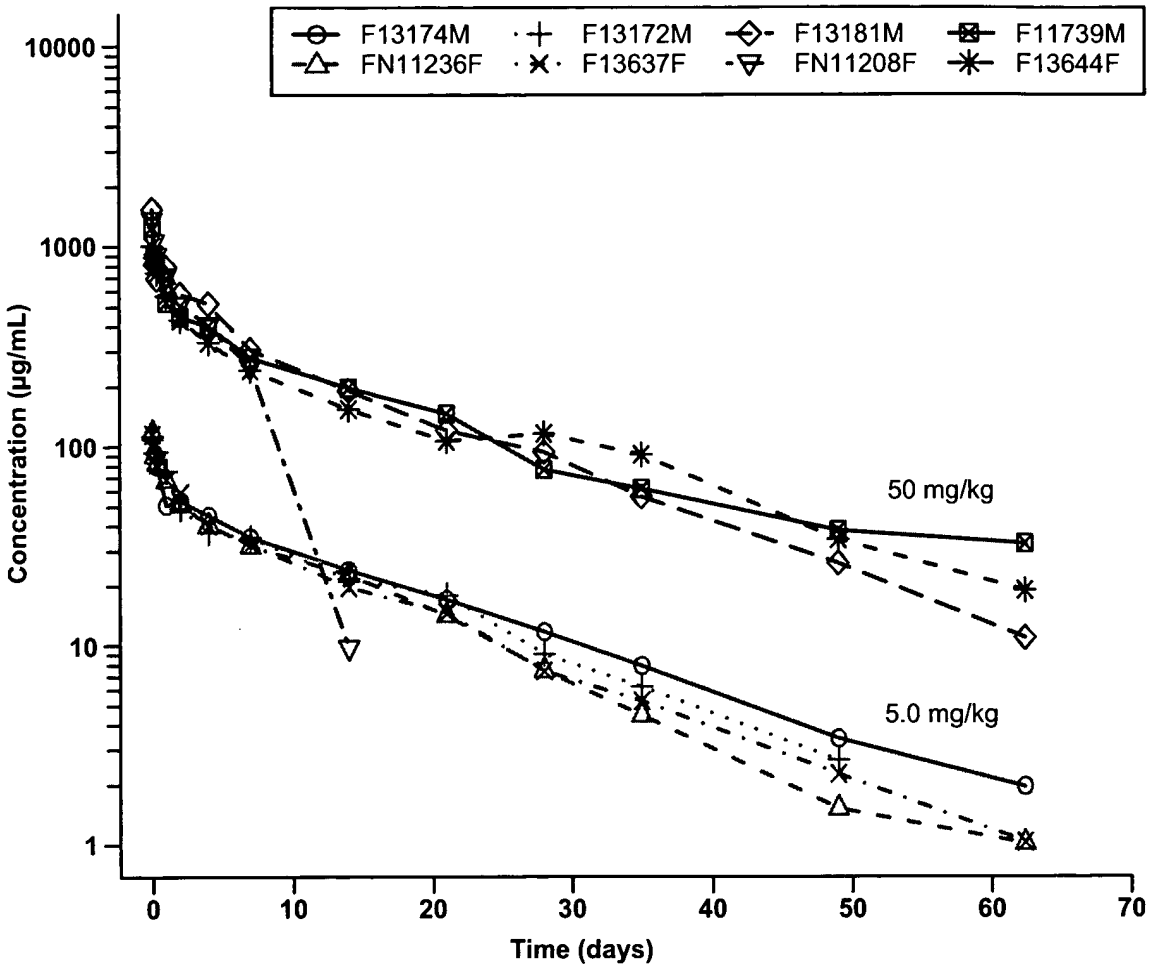

Figure 19 Serum concentration of LymphoStat-B in individual monkeys following iv injection of 5.0 or 50 mg/kg

Cynomolgus monkeys received a single iv injection of 5 or 50 mg/kg LymphoStat-B, and serum concentrations were measured over 9 weeks following injection. Monkey FN11208 in the 50 mg/kg dose group (FN11208F) showed significantly lower serum concentrations of LymphoStat-B after Day 8 and was excluded from the pharmacokinetic analysis. This animal was positive for anti-LymphoStat-B antibodies.

8.3.1.2 Interspecies Scaling of LymphoStat-B Pharmacokinetics from Cynomolgus Monkey to Human

The clearance of LymphoStat-B obtained from the single-dose pharmacokinetic study was scaled from a 3 kg monkey to a 70 kg human using the allometric equation ($Y = aW^b$) with an exponent of 0.75 (Mordenti et al, 1991). Intercompartmental clearance was also scaled using an exponent of 0.75, and volumes of distribution were scaled proportionally to body weight (exponent = 1). The predicted clearance in humans for LymphoStat-B is approximately 3 mL/day/kg, and the predicted terminal half-life (~26 days) is similar to the half-life of endogenous IgG in humans (18-23 days, Waldman and Strober, 1969). Predicted serum concentration curves for

LymphoStat-B in humans when given at the proposed Phase 1 doses of 1.0, 4.0, 10 and 20 mg/kg are shown in Figure 20.

The lowest dose for the proposed Phase 1 single-dose clinical trial of LymphoStat-B in SLE patients is 1 mg/kg administered iv. This dose is within the range of doses used for approved therapeutic mAbs (Breedveld, 2000). Based on the pharmacokinetics of LymphoStat-B in cynomolgus monkeys, it is expected that the doses proposed for the Phase 1 trial (1-20 mg/kg) will result in circulating levels of LymphoStat-B that are well in excess of the levels of endogenous BLyS in the plasma. The excess of LymphoStat-B over BLyS increases the likelihood of inhibiting BLyS in the tissues in addition to circulating BLyS.

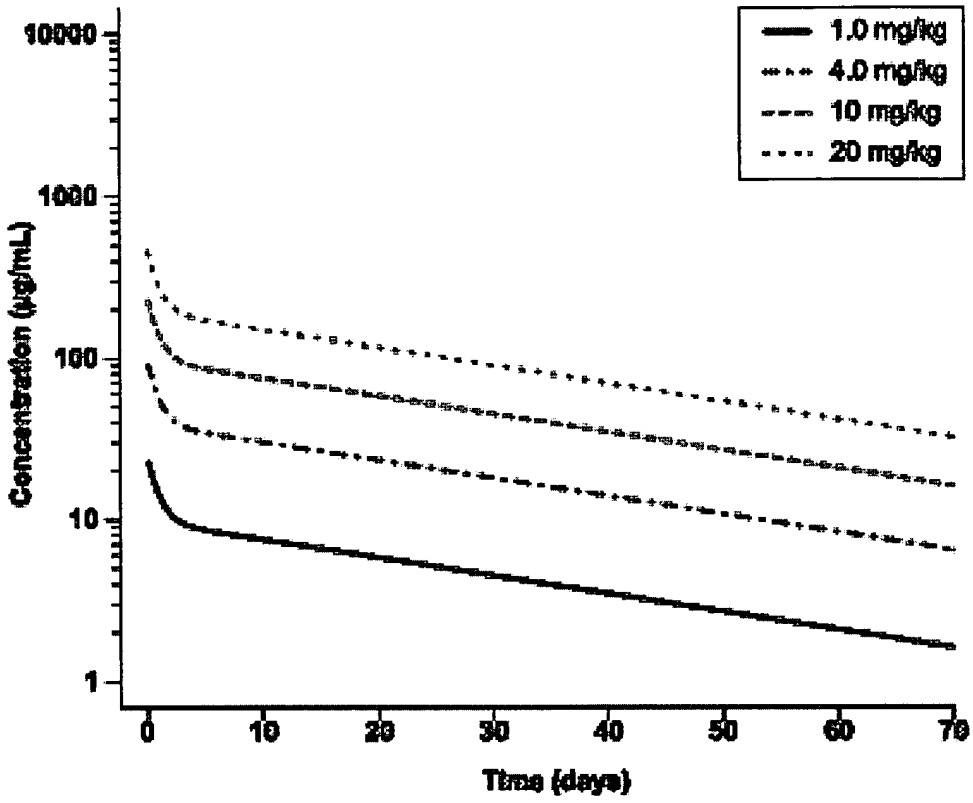

Figure 20 Predicted serum concentrations of LymphoStat-B in humans based on allometric scaling from monkey PK data

Serum concentrations of LymphoStat-B in humans were predicted by using allometric scaling (Mordenti et al, 1991) and a two-compartment pharmacokinetic model. Clearance and inter-compartmental clearance were scaled from a 3 kg monkey to a 70 kg human using an allometric exponent of 0.75, and volumes of distribution were scaled proportional to body weight (exponent = 1).

8.3.1.3 Conclusions from the Pharmacokinetic Studies

Based on the pharmacokinetic data, the following conclusions are drawn:

- The pharmacokinetics of LymphoStat-B in cynomolgus monkeys are independent of dose over the range of doses tested (5.0-50 mg/kg), and there are no significant differences between male and female monkeys.

- The terminal-half life of LymphoStat-B following ivinjection in cynomolgus monkeys is 11-14 days, the clearance is 5.6 mL/day/kg, and the steady-state volume of distribution is 85-107 mL/kg. The long half-life, slow clearance, and small volume of distribution relative to extracellular fluid are consistent with the expected pharmacokinetics of a large macromolecule such as a monoclonal antibody.

- The pharmacokinetics of LymphoStat-B after 4 iv doses in cynomolgus monkeys agree well with the pharmacokinetic parameters obtained following a single iv dose, indicating that the pharmacokinetics of LymphoStat-B do not appear to change after multiple doses.

- Based on allometric scaling from the cynomolgus monkey, the predicted clearance in humans for LymphoStat-B is approximately 3 mL/day/kg, and the predicted terminal half-life is similar to the half-life of endogenous IgG in humans.